REMARKS

In the Office Action mailed from the United States Patent and Trademark Office on June 30, 2004, the Examiner rejected claims 1-15, 17 and 19-23 under 35 U.S.C. § 112, Second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner further rejected claims 1-6, 11-15 and 19-22 under 35 U.S.C. § 102(b) ("Section 102(b)") as being anticipated by United States Patent No. 4,963,360 to Argaud ("Argaud"). Additionally, Examiner rejected claim 23 under 35 U.S.C. §103(a) ("Section 103(a)") as obvious in view of Argaud. The Examiner further objected to claims 7-10 and 17 as being dependent upon a rejected base claim, but indicated that claims 7-10 and 17 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Accordingly, Applicant respectfully provides the following:

1. Claim Rejection Under 35 U.S.C. § 112

In the Office the Examiner rejected Claims 1-15, 17, and 19-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner indicated that it was unclear to the Examiner what it meant by a "pre-determined duration of time."

"The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular set of matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed...in light of: (A) the content of a the particular application disclosure; (B) The teachings of the prior art; (C) The claim interpretation that would be given by one possessing ordinary level skill in the pertinent art at the time the invention was made." *Solemon v. Kimberly-Clark Corp.*, 216 F.3d 1372 (Fed. Cir. 2000); M.P.E.P. § 2173.02.

The first factor that should be considered in determining whether claim language is clear and precise is the content of the particular application's disclosure. The language "pre-determined duration of time" is a necessary element of the present invention and finds support in the specification. Being able to predetermine the duration of time over which a specified intensity of heat is generated by the present invention is critical for allowing the invention to supply an effective and safe dose of medication. That dose of medication depends on the type of medication used, the patient to which the medication is administered and the circumstances under which the medication is administered. The specification indicates the industry's need for an invention that produces a pre-determined duration and intensity of heat.

> It would be advantageous to...make use of DDDSs more flexible, controllable and titratable (varying the drug's delivery rate, amount or period according to the biological effect of the drug) to better accommodate various clinical needs...It would further be advantageous to develop means to alter mainly to increase the drug absorption rate from the storage sites or injection sites in such ways that can accommodate certain clinical needs. *Specification*, at 6-7.

Thus, the specification details the need for an invention that, as indicated in Claim 1, is capable of "controlled delivery of analgesic through a patient's skin ... comprising ... heating said skin with said temperature modification apparatus to a predetermined temperature range for a predetermined duration of time." *Claim 1*.

The specification further indicates structural characteristics of the present invention that allow heat to be produced for a "pre-determined duration of time."

> After removal from the air-tight container, oxygen in the atmosphere ("ambient oxygen") flows into heat generating medium through the areas on the non-air permeable top with desired air-permeability to initiate a heat generating oxidation reaction (*i.e.*, an exothermic reaction). The desired heating temperature and duration can be obtained by selecting the air exposure of the top (*e.g.*, selecting the right size and number of

> holes on the cover and/or selecting the microporous membrane covering the holes for a specific air permeability), and/or by selecting the right quantities and/or ratios of components of the heat generating medium. *See Specification,* at 14.

Thus, the specification indicates that based on particular clinical needs a practitioner can pre-determine the duration of heat produced by pre-selecting the size and number of holes on the cover and and/or by selecting the right quantities and/or ratios of components of the heat generating medium. Thus, the specification details an apparatus and methods to accomplish "heating said skin with said temperature modification apparatus to a predetermined temperature range for a predetermined duration of time."

The specification provides several specific embodiments for administering a pharmaceutical at predetermined temperature ranges for predetermined durations of time. FIG. 5 and Table A of the Specification detail results of experimentation, which demonstrate that given the size of the patch used, the number of holes and diameter of holes in the top surface utilized, a pre-determined temperature range was accomplished for a pre-determined of time. In Example 1, the temperature control apparatus was capable of keeping the patient's skin temperature at a narrow elevated range of about 41° C to 43 ° C for about 240 minutes. This embodiment represents one temperature range, and one duration of time using the present invention. In another embodiment of the present invention experimental results indicated that the temperature control apparatus was cable of keeping skin temperature to a narrow, elevated range of between 41° and 44° Celsius for about 450 minutes. *See Specification*, at 27. Other embodiments of the present invention wherein the physical structure of the invention is modified to obtain a predetermined temperature range for a predetermined duration of time are described. *See Specification*, at 30-65.

The specification details the use of the present invention with specific pharmaceuticals. Each pharmaceutical is utilized to affect each patient's unique diagnostic traits. Consequently, each pharmaceutical has a unique administration profile, which requires a manufacture to pre-determine the duration and intensity of heat provided by the current application. Example two of the specification details one embodiment of the present invention wherein administration of fentanyl is used to treat breakthrough pain. Delivering a specific therapeutic range of a pharmaceutical is critical to clinical efficacy and insuring patient safety when analgesics like fentanyl are administered. Patient overdose is a serious danger that requires precise control of the intensity and duration of heat when pharmaceuticals are administered by heated dermal apparatus. Alternatively, insufficient intensity and duration of heat applied to systems for dermal administration of pharmaceuticals result in the pharmaceutical being administered below its therapeutic range, which provides little or no benefits to the patient. Therefore, it is important to control the intensity and duration of heat precisely.

Example three, which describes the administration of nicotine, of the specification further details the need for being able to produce heat for a pre-determined temperature ranges for pre-determined durations of time. The use of a heated patch for administration of fentanyl, and the use of a heated patch for the administration of nicotine require different temperature ranges and different durations of time. Thus, a manufacture utilizing the present invention must be able to pre-determine the temperature range, and pre-determine the duration of time over which the administration of the active pharmaceutical will be affected by the present invention.

The Specification is filled with examples of the present invention being used for various therapeutic purposes, each requires a different heat and duration profile. Example four of the specification provides another embodiment of the present invention wherein the present

invention is utilized to administer testosterone to mimic circadian rhythms, which requires a pre-determined temperature range and duration. Example five provides an example of the present invention wherein a temperature control apparatus can be used with athletic injuries. Example six is yet another example of using an embodiment of the present invention for administering analgesic to treat pain wherein the analgesics have particular diffusion coefficients across rate limiting membranes. Example seven is still another example of using an embodiment of the present invention for decreasing the onset time of an analgesic material from a DDDS. Thus, the specification is filled with examples of embodiments of the present invention wherein the present invention is used for various therapeutic purposes. Each therapeutic purpose will requires the present invention to produce heat to a predetermined temperature range for a predetermined duration of time for the therapeutic advantages of the treatment to be actualized. Consequently, the claim language "heating said skin for a predetermined duration of time" is a necessary element of the present invention that allows the present invention to be utilized in various therapeutic settings and for various therapeutic needs.

The M.P.E.P indicates that "[d]efiniteness of claim language must be analyzed...in light of...the claim interpretation that would be given by one possessing ordinary level skill in the pertinent art at the time the invention was made." *Solemon v. Kimberly-Clark Corp.*, 216 F.3d 1372 (Fed. Cir. 2000); M.P.E.P. § 2173.02. Mirriam-Webster's dictionary defines predetermine as "to determine beforehand" or "to impose a direction or tendency on beforehand;" duration as a "continuance in time" or "the time during which something exists or lasts;" and time as "the measured or measurable period during which an action, process, or condition exists or continues." Thus, the dictionary defines a "pre-determined duration of time" as a determined beforehand continuance of time during which something lasts. A manufacture determines

beforehand the continuance of time during which heat will be applied for the administration of a particular pharmaceutical by selecting the physical characteristics of the present invention, including selecting the right size and number of holes on the cover and/or selecting the microporous membrane covering the holes for a specific air permeability, and/or by selecting the right quantities and/or ratios of components of the heat generating medium.

2. Claim Rejection Under 35 U.S.C. § 102(b)

Claims 1-6, 11-15 and 19-22 stand rejected under 35 U.S.C. § 102(b) ("Section 102(b)") as being anticipated by United States Patent No. 4,963,360 issued to Argaud ("Argaud"). Specifically the Examiner indicates that "Argaud discloses a method for improving the absorption performance of the medicinal components to be applied to the skin; the absorption performance is generally accelerated through warming comprising an exothermic packaging body having a layer containing medicinal component. It is the Examiner's position that the exothermic layer will heat the patient's skin since that temperature is higher than the body temperature."

An invention is unpatentable under 35 U.S.C. § 102(b) if "the invention was patented or described in a printed publication . . . more than one year prior to the date of application for patent in the United States." A 35 U.S.C. § 102(b) rejection is only appropriate where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); M.P.E.P. § 2131. In addition, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); *M.P.E.P.* § 2131. For the reasons set forth below, Applicant submits that the reference cited by the Examiner neither teaches each and every element of the claimed invention, nor shows the

identical invention in as complete detail as in Applicant's claims, and thus does not anticipate the present invention.

Delivering a specific therapeutic range of a pharmaceutical is critical to clinical efficacy, and ensuring patient safety. The dermal administration of pharmaceutically active compounds has long been known in the practice of medicine, and continues to be an important technique in the delivery of pharmaceutically active compounds. It is known that elevated temperatures can increase the absorption of drugs through the skin. This much Argaud disclosed. What was still needed was an improved drug administration system. More specifically, dermal drug delivery systems needed to be more flexible, controllable and titratable to better accommodate various clinical needs. Delivering a specific therapeutic range of a pharmaceutical is critical to clinical efficacy, and ensuring patient safety. Patient overdose is a serious danger that requires precise control of the intensity and duration of heat when pharmaceuticals are administered by a heated dermal apparatus. Alternatively, insufficient intensity and duration of heat applied to systems for dermal administration of a pharmaceutical results in the pharmaceutical being administered below its therapeutic range, which provides little or no benefit to the patient. Therefore, it is important to control the intensity and duration of heat precisely.

The present invention claims elements not taught in Argaud. The present invention claims a package body that is capable of controlling the magnitude and duration of heat produced by an exothermic package or other heat source. The present invention claims "a method of *controlled* delivery of analgesic" (emphasis added) comprising a "temperature modification apparatus designed to deliver a particular dose of a drug at a *pre-determined* temperature range for a *pre-determined* duration of time, to deliver an appropriate amount of the drug." (emphasis added) See *Claim 1.* In addition, the present invention claims "a temperature control apparatus

secured to said patch, said temperature control apparatus being capable of heating said patch and said patient's skin proximate said patch to a *pre-determined* range for *a pre-determined* duration of time." (emphasis added) See *Claim 22.* The claims utilize the language "controlled" and "pre-determined" to emphasize the control element of the present invention that are critical to safe and effective pharmaceutical administration. "Controlled" and "pre-determined" are claim elements that are not taught in the prior art.

The specification describes the need for control, provides lengthy descriptions of the elements of the present invention that allow for control and provides multiple embodiments of the present invention that illustrate the concept of control claimed in the present invention:

> [t]he present invention is specifically engineered to provide a *predetermined* amount of heat for a *predetermined* time, thus precisely controlling the dosage of medicine administered to a given patient. Based on experimental data, the temperature modification apparatus has been designed to deliver *precise control* over intensity and duration of heat produced. One embodiment of a *controlled* heat generating apparatus is a shallow chamber including non-air permeable side wall(s), a bottom wall, and a non-air permeable top wall which has area(s) with limited and desired air permeability (e.g., holes covered with a micro porous membrane)...*The desired heating temperature and duration can be obtained by selecting the air exposure of the top (e.g., selecting the right size and number of holes on the cover and/or selecting the micro porous membrane covering the holes for a specific air permeability), and/or by selecting the right quantities and/or ratios of components of the heat generating medium.* (emphasis added) *Specification,* at 13- 14.

The elements of control claimed in "method of controlled delivery" of claim 1 and the "temperature control apparatus" of claim 22 result from specific structural features of the present invention not present in Argaud. The present invention is a closed system, whereas Argaud is an open system. The present invention utilizes non-air permeable barriers to strictly control the amount of oxygen that is exposed to the exothermic package. Argaud's invention allows oxygen to enter uncontrolled into the system. Argaud teaches an exothermic package separated from oxygen only by an air permeable bag. Argaud teaches an invention that exposes the exothermic

package exposed to oxygen along its entire surface area. The present invention claims a titrated exothermic reaction tightly separated from oxygen by air impermeable barriers. The closed system of the present invention, isolated from oxygen, is exposed with mathematical precision to oxygen by carefully controlling specific parameters: "selecting the right size and number of holes on the cover and/or selecting the micro porous membrane and covering the holes for specific air permeability, and/or by selecting the right quantities and/or ratios of components of the heat generating medium." *Specification*, page 13 lines 24-27 and page 14 lines 5-10. Since the amount of heat generated is determined by the amount of surface area of the exothermic package exposed to oxygen, the amount of heat generated can be varied in embodiments of the present invention as the amount of surface area exposed to oxygen is varied. More holes allow more oxygen to flow through the microporous membrane; less holes allow less oxygen to flow through the microporous membrane. Increasing the diameter of holes in the cover allows more oxygen to flow through the microporous membrane; decreasing the diameter of the holes in the cover allows less oxygen to flow through the microporous membrane. Thus, by varying the amount of surface area exposed to oxygen, the amount of heat generated is controlled.

The detailed description of the present invention provides significant scientific data regarding the size and number of holes used to produce specific temperatures for specific durations of time. *Examples 1-28 in the Specification, pages 21-64.* The specification specifically denotes physical structures, which produce pre-determined temperature ranges for pre-determined duration of time. Pages 13-14 of the Specification describe the concept of varying the physical structure of the present invention to control the flow of oxygen over the exothermic package (see block quote supra).

Page twenty of the Specification provides a lengthy description of a preferred embodiment of the present invention, which allows for pre-determined controlled air flow over the exothermic package:

> FIG. 2 illustrates a temperature control apparatus 100 comprising a temperature regulating mechanism 108 surrounded by a bottom wall 102, a top wall 104, and side walls 106...The top wall 104 is preferable also a flexible non-air permeable material having holes 114 there through. An air permeable membrane 116 is preferably, disposed between the top wall 104 and the temperature regulating mechanism 108 to regulate the amount of air reaching the temperatures regulating mechanism 108 through the holes 114. The air permeable membrane 116 is preferably a porous film (such as No. 9711 microporous polyethylene film-CoTran™, 3M Corporation, Minneapolis, Minnesota, USA.) *Specification,* at 20.

Example 1 of the specification details the use of physical structures to control the rate at which oxygen contacts the temperature regulating mechanism and provides a preferred embodiment of the mechanism:

> [o]xygen in ambient air flows into the temperature regulating mechanism 108 through holes 114 and air permeable membrane 116. Of course, it is understood that the rate at which oxygen contacts the temperature regulating mechanism 108 is determined by the size and number of holes 114 on the top wall 104, as well as the air permeability of the air permeable membrane 116...In actual experimentation, the temperature control apparatus 100 comprised the side walls 106 defined by a 1/8 inch thick rectangular foam tape (2 layers of No.1779 1/16" white foam tape, 3M Corporation, Minneapolis, Minnesota, USA) with an outer dimension of about 2.25 inches by 4 inches with an opening therein having an inner dimension of about 1.75 inches by 3.5 inches, the bottom wall 102 comprising rectangular medical tape...of a dimension of about 2.25 inches by 4 inches with a non-adhesive side attached to the bottom of the side walls 106, and a top wall 104 comprising a rectangular 1/32 inch thick foam tape...with forty-five holes 114 (diameters approximately 0.9 mm, in a 5 by 9 pattern with about 7.5 mm to 8.0 mm center spacing) therethrough. The side walls 106, the bottom wall 102, and the top wall 104 defined a chamber. The holes 114 of the top wall 104 were covered by an air permeable membrane 116 comprising a porous membrane...disposed between the top wall 104 and the temperature regulating mechanism 108...The temperature control apparatus 100 was tested on a volunteer...The results of this temperature control apparatus 100 is capable of keeping the skin temperature to a narrow, elevated range of about 41°C to 43°C for extended period of time (at least about 240 minutes). *Specification*, at 21-22.

Example 1 of the Specification details substantial research, which demonstrates that the present invention is capable of precisely controlling the flow of oxygen over the exothermic package:

> [i]n yet another experiment, the temperature control apparatus 100 comprised the side walls 106 defined by a 3/16 inch thick rectangular foam tape with an outer dimension of about 2.25 inches by 4 inches with an opening therein having an inner dimension of about 1.75 inches by 3.5 inches, the bottom wall 102 comprising rectangular medical tape of a dimension of about 2.25 inches by 4 inches with a non-adhesive side attached to the bottom of the side walls 106, and a top wall 104 comprising a rectangular 1/32 inch thick foam tape with seventy-eight holes 114 therethrough (diameters approximately 1/32 inch, in a 6 by 13 pattern with about a 6 mm center spacing). This temperature control apparatus 100 was tested on a volunteer's stomach with a temperature probe placed between the temperature control apparatus 100 and the volunteer's skin to measure the temperature. The results of this temperature experiment is illustrated in FIG. 7 and Table C, which shows that the temperature control apparatus 100 is capable of keeping the skin temperature to a narrow, elevated range at between about 41 and 44°C for extended period of time (at least about 450 minutes). *Specification*, at 21-29.

The ability to control the intensity and duration of heat produced is necessary for precise and accurate pharmaceutical administration. The temperature modification apparatus of the present invention is capable of administering analgesics over a long period of time (e.g., 240 minutes disclosed in Example 1), and over a short period of time (e.g., 15 minutes disclosed in Example 3). *Specification*, at 32. In addition, the temperature modification apparatus is capable of keeping the skin temperature within various selected ranges. *Specification, page 22, lines 25-26; page 34, lines 18-20.* The ability to control the temperature rage and duration of time improves the administration of analgesics by more effectively treating a variety of pains, illnesses, injuries and addictions, including localized pain, nicotine addiction, athletic injuries, cancer pain, inflammations, hypertension, depression, diabetes, migraines, asthma, obesity, and nausea. This ability to control the intensity and duration of heat produced is necessary for

customizing treatments, especially because different people react differently to the same drugs. Exercising accurate control over the drug delivery process is essential to the safety and health of the patient.

The specification details the ability of the present invention to control the time and rate at which heat is generated, which allows for the improved administration of pharmaceuticals. Example seven of the Specification provides an embodiment of the present invention to decrease the onset time of an analgesic material:

> [t]he heat from the temperature control apparatus 150 increases the temperature at a contact surface of the skin 134 and the DDDS 160, 165 to temperatures up to about 60°C, preferably a narrow temperature range between about 36°C and 46°C, most preferably between 37°C and 44°C, and maintains this temperature for a period of time (*i.e.*, approximately 4 hours). *Specification*, at 34.

Example 9 details a method for utilizing one embodiment of the present invention for decreasing onset time, "wherein the temperature control apparatus 150 is capable of providing heating the skin to a narrow range between about 37°C and 41°C, preferably between 39°C and 40°C, for at least 30 minutes." *Specification*, at 36. Example 11 details the need for a pre-determined duration and intensity of heat:

> [c]ertain drugs have relatively low therapeutic indices, meaning that the differences between the therapeutic dose and the dose which can cause serious and/or undesired side effects are small. Thus, dermal delivery of such drugs can be dangerous (over-dose) or ineffective (under-dose), especially for individuals whose skin are exposed to highly variable ambient temperatures, such as people working outdoors in extreme weather conditions. *Specification,* at 38.

Example 11 then provides significant detail regarding the physical structures of the present invention and methods for manipulating those physical structures that yield the element of control claimed by the present invention:

> [t]his embodiment of the present invention is accomplished by varying in detailed fashion the detailed structure of the present invention. The specification on page 38 line 26 through pg 40 line 16 details variation in the type of air permeable

surface that separates the exothermic package from oxygen. Further, the specification details the use of a covering with a plurality of holes for the regulation of air into chambers, and a second covering, which has an opening to expose a certain number of holes for the regulation of air into the packaging. ...FIGs. 13-19 illustrates another embodiment of a temperature control apparatus 170. FIG. 13 illustrates the temperature control apparatus 170 which is similar to the embodiment of FIG. 8, but comprises a temperature regulating mechanism 108 which is made up of a plurality of chambers 172 separated by non-air permeable walls 174. The temperature regulating mechanism 108 is substantially surrounded by a bottom wall 102, a top wall 104, and side walls 152. Again, the temperature regulating mechanism 108 preferably comprises a composition of activated carbon, iron powder, sodium chloride, water, and, optionally, saw dust, which is disposed in each of the chambers 172. The top wall 104 is preferably also a flexible non-air permeable material having a plurality of holes 114 therethrough, preferably, a row of holes 114 for each chamber 172. An air permeable membrane 116 is disposed between the top wall 104 and the temperature regulating mechanism 108 to regulate the amount of air reaching the temperature regulating mechanism 108 through the holes 114. The top wall 104 can have at least one cover covering the plurality of holes 114 for the regulation of the air into the chambers 172. As illustrated in FIG. 13, three covers are layered on the top wall 104. A first cover layer 176 is affixed to the top wall 104 and has openings 178 (see FIG. 17) to expose 2 out of 3 holes 114. A second cover layer 182 is affixed to the first cover layer 176 and has opening 184 (see FIG. 15) to expose 1 out of 3 holes 114. A top cover 186, which has no openings, is affixed to the second cover layer 182. Thus, a patient has a various opinions on what percentage of chambers 172 to expose to ambient air. If the heat generated from one third of the chambers is required, the top cover 186 is removed, as shown in FIGs. 14 and 15. If the heat generated from two thirds of the chambers is required or if another additional heat is needed after the depletion of the first one-third of the temperature regulating mechanism 108, the top cover 186 and the second cover layer are removed, as shown in FIGs. 16 and 17. If the heat generated from all of the chambers is required or if another additional heat is needed after the depletion of the first and second one-third of the temperature regulating mechanism 108, the top cover 186, the second cover layer 182, and the first cover layer 176 are removed, as shown in FIGs. 18 and 19. It is, of course, understood that more or less cover layers can be used with any number of holes to results in any desired amounts of the temperature regulating mechanism 108 being activated.

Thus, by way of example a patient can have a number of choices in using the temperature control apparatus 170, such for the suppression of breakthrough pain. When the breakthrough pain occurs, the patent places the temperature control apparatus 170 over an analgesic material DDDS and can do any of the following:

1) Activate a particular number or percent of chambers 172 by removing the requisite covers depending on how much additional analgesic material is required to treat the breakthrough pain. The covers can be preferably

replaced to stop the exothermic reaction when no more additional analgesic material is required.

2) Activate a particular number or percent of chambers 172, exhaust the heat generating capacity of those chambers 172, and then activate other (non-activated) chambers 172. This extends the heating duration of the temperature control apparatus 170. The duration of the total heating time is determined by the typical duration of the particular patient's breakthrough pain.

3) Activate enough chambers 172 to treat one episode of breakthrough pain, and leave the heating patch in place. When the next episode of breakthrough pain occurs, activate unused chambers 172." *Specification*, at 39-40.

Thus, the specification describes exacting physical structures that produce titrated levels of control over the flow of oxygen through holes in the top wall and into contact with the exothermic package. This embodiment of the present invention is an example of producing predeterimined temperatures for predeterimined durations of time.

Argaud fails to teach every element of the claimed invention. Argaud does not teach controlled air flow, and thus Argaud teaches an uncontrolled heating source. Argaud fails to teach the claim limitations "[a] method of *controlled* delivery...comprising...a temperature modification apparatus ....capable of *controlling and selectively modifying a magnitude and duration of heat to achieve selective precise, on-demand delivery of said analgesic*...and heating said skin...to a *pre-determined* temperature range for a *pre-determined* duration of time." Claim 1. Argaud teaches an exothermic package, which provides heat when exposed to air, attached to a layer that carries medicine, to enhance absorption of medicine through the skin. The concept of "control" is absent from Argaud's teachings. Argaud does not teach any means for modifying the intensity or duration of heat produced. Argaud does not teach a package body itself that is capable of controlling the magnitude and duration of heat produced by the package. Argaud does not disclose an apparatus or method for strictly limiting the amount of heat that is generated in the exothermic reaction. Argaud does not teach preparing and deciding beforehand what the

appropriate dosage should be. Because Argaud neither actively controls the surface area of the exothermic layers exposure to oxygen, the exothermic medium's shape, nor the amount of heat generated. Argaud is simply an on-off-switch; when it is removed from its packaging it is fully exposed to air and when it is removed from the skin it is no longer capable of administering a pharmaceutical.

Argaud did not indicate potent or particularly dangerous drugs because there is significant risk of overdose when using an uncontrolled heat source to increase the absorption of drug through the skin. When used with more potent drugs, such as those drugs used in the present invention it would only be safe to use heat if the amount of heat and the duration of heat could be strictly controlled. *Specification, p. 37, lines 23-29 and p. 38, lines 1-5.* Applicant respectfully submits that Argaud fails to teach a delivery systems that allows for the manufacture to adjust timing of administration and that Argaud fails to teach a delivery system that allows for precise and accurate control of duration and intensity of heat. The present invention claims means for controlling the timing the administration of a pharmaceutical. Claim 23 claims a "step of applying a temperature modification apparatus proximate to said delivery site on said skin" that is "performed when said patient starts to feel the onset of breakthrough pain." Because Argauds patch is an integrated heating and medicine patch the user cannot apply the pharmaceutical dermally then subsequently apply the heating elements of Argaud when break through pain is experienced. Either the Argaud patch is applied to the skin, pharmaceutical and heating patch, or it is not. The control claimed in the present invention is particularly evident in one disclosed embodiment of the present invention where a non-air permeable top wall with holes is used to control the rate of drug delivery. See *Specification, page 20, lines 20-21.* One way the present invention functions to increase the rate at which the drug is delivered is to

uncover additional holes, exposing the exothermic layer to more oxygen, which in turn raises the temperature and increases the rate at which the drug is delivered.

Argaud does not teach any means of regulating the rate of which oxygen interacts exothermically with the exothermic layer of the package. While Argaud discloses an apparatus capable of increasing drug administration rates, the apparatus itself fails to implement any feature that enables specific temperature regulation capable of precisely controlling and possibly reducing rates of drug delivery, as claimed by the present invention. Oxygen is the fuel that allows the heat producing exothermic reaction to occur. Argaud does not teach any means of regulating the rate at which oxygen interacts exothermically with the exothermic layer of the package. The detailed description of the preferred embodiments of the Argaud patent indicate that element 3, FIG. 1 is a cover film. FIG. 1 further depicts layers 5 and 6 wherein layer 5 is an air permeable cover film and 6 is packaging material. Thus, the Argaud patent describes an invention wherein an exothermic layer is separated from the limiting agent, oxygen, by air impermeable packaging material and an air permeable film. When the packaging material is removed from Argaud's invention the exothermic layer is separated from oxygen only by an air permeable cover-film. Argaud does not disclose or teach structural elements that allow for controlling the amount of oxygen that is exposed to the top surface area of the exothermic package. Specifically, Argaud does not teach varying the number of pores or the size pores through which oxygen may come in contact with an air permeable membrane. Argaud does not teach that a user may control the amount of heat applied by the exothermic package body by varying the duration of time that that package is exposed to oxygen. Argaud does not teach that the amount of heat applied could be varied by the duration of time that the package is applied to

the patient of interest. Argaud does not teach a package body itself that is capable of controlling the magnitude and duration of heat produced by the package.

A package body capable of controlling the magnitude and duration of heat is not inherent in Argaud's disclosure. As previously discussed the Argaud patent claim an invention wherein the exothermic package is separated from the limiting reagent, oxygen, only by an air permeable membrane. Argaud does not teach a package body capable of controlling the magnitude and duration of heat produced. Where oxygen is the limiting reagent it might be tempting to assume that with increased duration of exposure to oxygen the exothermic layer will produce more heat for a longer period of time. Additionally, it might be tempting to assume that with more exothermic reagent placed in the exothermic layer, more heat would be produced for a longer period of time. These simplifying assumptions are flawed. The amount of heat produced, and the duration of the reaction in this case are complicated by factors beyond duration of exposure to oxygen. One such complicating factor is proximity. Oxygen is only exposed to the exothermic reaction along the surface area of the exothermic reactants. As additional exothermic reagents are added to the package the volume of the package increases at a cubed rate, while the surface area of the package increased at a squared rate, of which only a portion is exposed to oxygen. The remainder does not react. Thus, increased volumes of reactants placed in the exothermic package do not correlate directly with changes in intensity and duration of heat produced, providing an unreliable and less predictable means of affecting intensity and duration of heat produced. Because these simplifying assumption are unreliable, Argaud fails to disclose a temperature modification apparatus capable of achieving selective, precise, on-demand delivery of an analgesic through the skin, as claimed by the present application. Even if the simplifying

assumptions produced reliable results it would be inappropriate to impute those assumptions into Argaud's disclosure; Argaud does not teach the principle of control.

Based on the foregoing, Applicant respectfully submits that Argaud does not anticipate any of the claims of the present invention. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 102 be withdrawn. Dependent claims 2-6, 11-15, and 19-22 place further limitations on what is otherwise argued allowable subject matter. Therefore, Applicant respectfully submits that these claims stand in a condition for allowance.

3. Claim Rejection -- 35 U.S.C. § 103(a)

Claims 1, 19 and 23 stand rejected under 35 U.S.C. §103(a) ("Section 103(a)") as obvious in view of Argaud. An invention is unpatentable under Section 103(a) "if the differences between the subject matter sought to be patented over the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." To establish a *prima facie* case of obviousness, three criteria must be met. "First, there must be some suggestion or motivation . . . to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142. For the reasons set forth below, Applicant submits that the reference cited by the Office neither provides a suggestion or motivation to modify, nor does the prior art teach all of the claim limitations, and thus does not anticipate the present invention.

Argaud does not teach all of the claim limitations of the present invention. As previously discussed, a comparison of Argaud and the present invention reveals important differences. The "method of controlled delivery" claim 1 and the "temperature control apparatus" of claim 22

result in a system, that allows a practitioner to administer pharmaceuticals under conditions where the heating of skin can be set at a predetermined temperature range for a predetermined duration of time, whereas Argaud is an open system, wherein oxygen freely contacts the entire surface area of the exothermic package through an air permeable membrane. In the closed system of the present invention, the amount of oxygen that enters the system is actively controlled by the number and size of pores selected. In Argaud, oxygen enters uncontrolled into the system through an air permeable membrane across the entire surface area of the exothermic package. Because the intensity and duration of heat generated is determined, in part, by the amount of surface area exposed to oxygen, the amount of heat generated in the present invention can be varied in embodiments of the present invention as the amount of surface area exposed to oxygen is varied. Thus, by varying the amount of surface area exposed to oxygen, the amount of heat generated is controlled. The amount of surface area of the exothermic package in the present invention is dictated by the number and size of holes selected. In contrast to the controlled exposure to oxygen in the present invention, Argaud teaches the uncontrolled exposure to oxygen as oxygen freely enters through the air-permeable film. *Argaud, Claims 1 and 3.* Consequently, Argaud neither actively controls the surface area's exposure to oxygen, the exothermic medium's shape, nor the amount of heat generated.

One skilled in the art would not have been motivated to control the delivery of the medicinal component because no control mechanism existed to modify the exposure to oxygen. In fact, it is an impermissible form of hindsight analysis to presume that the Argaud reference taught that one could control the intensity and duration of heat by varying the quantity of exothermic medium utilized. Argaud does not teach or suggest the claim limitation of controlling the intensity or duration of heat generated in any fashion. Particularly, Argaud does not disclose,

nor is there any discussion regarding varying the quantity of exothermic medium utilized for a given patch.

While Argaud discloses an apparatus capable of increasing drug delivery rates, the apparatus itself fails to implement any features, which enable specific temperature regulation for precisely controlling the rate of delivery of a pharmaceutical as claimed by the present invention. Claim 1 of the present invention as amended, recites "a temperature modification apparatus capable of controlling and selectively modifying a magnitude and duration of heat to achieve selective, precise, on-demand delivery of said analgesic through said skin." Applicant finds no mention or suggestion of these elements in the cited references, nor any equivalent thereof.

Indeed, although Argaud discloses an apparatus capable of increasing drug absorption performance, Argaud neither discloses nor suggests an apparatus having a temperature regulation system that achieves selective, precise, on-demand drug delivery, as claimed by the present application. Instead, Argaud emphasizes the ability of the exothermic layer to develop heat when brought into contact with air, thereby increasing drug delivery rates. Argaud, however, fails to mention or suggest that the apparatus may control, and possibly limit, such drug delivery rates.

Finally, Applicant respectfully submits that claim 23, which claims the "step of applying a temperature modification apparatus proximate to said delivery site on said skin" that is "performed when said patient starts to feel the onset of breakthrough pain," is not obvious because of the control and speed required for effective treatment after the onset of breakthrough pain. This is evident in one disclosed embodiment of the present invention where a non-air permeable top wall with holes is used to control the rate of drug delivery. See *Specification, page 20, lines 20-21.* One way the present invention functions to increase the rate at which the drug is

delivered is to uncover additional holes, exposing the exothermic layer to more oxygen, which in turn raises the temperature and increases the rate at which the drug is delivered.

Applicant respectfully submits that Argaud does not teach or suggest the limitations taught in claim 23 discussed above. In particular, one skilled in the art of analgesic administration would not think to introduce the control of the present invention. Accordingly, Applicant respectfully requests withdrawal of the Examiner's rejections of claim 23 as obvious in view of Argaud under Section 103(a).

CONCLUSION

Applicants submit that the amendments made herein do not add new matter and that the claims are now in condition for allowance. Accordingly, Applicants request favorable reconsideration. If the Examiner has any questions or concerns regarding this communication, the Examiner is invited to call the undersigned.

DATED this 29 day of September, 2004.

Respectfully submitted,

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